CLAIMS

What is claimed is:

1. A method of deriving a peptidomimetic of a biologically active metallopeptide comprising the steps of:

(a) selecting a biologically active metallopeptide, the metallopeptide comprising at least a peptide sequence with a metal ion complexed thereto, wherein biological activity is related to at least two elements of such metallopeptide, the at least two elements independently comprising an amino acid residue, amino acid side chain moiety or derivative thereof, and wherein the metal ion is complexed to at least three atoms in the peptide sequence, such at least three atoms being part of at least two amino acid residues comprising the peptide sequence, whereby such at least three atoms and the metal ion form a ring structure comprising at least one ring, the at least one ring of the ring structure defining a template space;

(b) modeling a non-peptidic ring structure that is superimposable on the template space defined by at least one ring of the ring structure of the biologically active metallopeptide; and

(c) forming a peptidomimetic by adding to the non-peptidic ring structure at least two elements independently comprising an amino acid residue, amino acid side chain moiety or derivative thereof, such at least two elements occupying a similar descriptor space as corresponding elements of the biologically active metallopeptide.

2. The method of claim 1, further comprising the step of comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide.

3. The method of claim 1 wherein the metal ion is a tetradentate metal ion and the metal ion is complexed to four atoms in the peptide sequence.

4. The method of claim 3 wherein the at least four atoms comprise an N_3S_1 ligand.

5. The method of claim 3 wherein the at least four atoms comprise an N_2S_2 ligand.

6. The method of claim 1 wherein at least one amino acid residue of the at least two amino acids residues of the biologically active metallopeptide to which the metal ion is complexed is an L- or D-3-mercapto amino acid.

7. The method of claim 6 wherein the L- or D-3-mercapto amino acid is L- or D-cysteine, L- or D-penicillamine, 3-mercapto phenylalanine, or a homologue of any of the foregoing.

8. The method of claim 1 wherein the metal ion is an ion of V, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Y, Mo, Tc, Ru, Rh, Re, Pd, Ag, Cd, In, Sn, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Po, At, Sm, Eu or Gd.

9. The method of claim 1 wherein the biologically active metallopeptide binds to a target of interest.

10. The method of claim 9 wherein the target of interest is a receptor, antibody, toxin, enzyme, hormone, nucleic acid, intracellular protein domain of biological relevance or extracellular protein domain of biological relevance.

11. The method of claim 1 wherein the template space of the metallopeptide is defined by fewer than all rings comprising the ring structure of the biologically active metallopeptide.

12. The method of claim 1 wherein the ring structure of the biologically active metallopeptide comprises a tricyclic ring structure.

13. The method of claim 12 wherein the template space is defined by one ring of the tricyclic ring structure.

14. The method of claim 12 wherein the template space is defined by two rings of the tricyclic ring structure.

15. The method of claim 1 wherein the ring structure of the biologically active metallopeptide comprises a 5,5,5-membered, 5-5-6-membered or 6-5-5-membered ring structure.

16. The method of claim 1 wherein the at least two elements and the defined template space of the biologically active metallopeptide define at least a portion of a pharmacophore.

17. The method of claim 1 wherein the at least two elements independently derived from an amino acid residue or amino acid side chain moiety of the biologically active metallopeptide comprise a

naturally occurring amino acid, a synthetic amino acid, a modified amino acid, a side chain of an a naturally occurring amino acid, a side chain of a synthetic amino acid, a side chain of a modified amino acid, a derivative of a side chain of a naturally occurring, synthetic or modified amino acid or a mimetic of any of the foregoing.

18. The method of claim 1 wherein the defined template space of the biologically active metallopeptide is defined, at least in part, by the coordination geometry of the metal ion.

19. The method of claim 2 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises comparison to the biological activity of a third compound.

20. The method of claim 2 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises screening for binding to the target of interest of claim 9.

21. The method of claim 20 where screening comprises competing a known binding partner for binding to the target of interest with the peptidomimetic.

22. The method of claim 2 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises a functional assay.

23. The method of claim 2 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises a biological receptor capable of transmitting a signal, and comparing further comprises determining whether the peptidomimetic induces transmission of the signal.

24. The method of claim 2 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises a biological receptor capable of transmitting a signal, and comparing further comprises determining whether the peptidomimetic inhibits transmission of the signal in the presence of a binding partner to the target of interest known to induce transmission of the signal.

25. The method of claim 1 wherein the biologically active metallopeptide is an agonist.

26. The method of claim 1 wherein the biologically active metallopeptide is an antagonist.

27. The method of claim 1 wherein the biologically active metallopeptide is specific for one or more melanocortin receptors.

28. The method of claim 1 wherein the biologically active metallopeptide is specific for an angiotensin receptor.

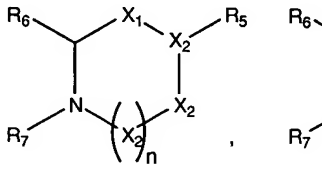
29. The method of claim 1 wherein the biologically active metallopeptide is specific for a vasopressin receptor.

30. The method of claim 1 wherein the biologically active metallopeptide is specific for an oxytocin receptor.

31. The method of claim 1 wherein the non-peptidic ring structure comprises a 5-, 6-, 7-, or 8-membered ring, a 5-5-, 5-6-, 5-7-, 5-8-, 6-6-, 6-7-, 6-8-, 7-7-, 7-8-, or 8-8-fused bicyclic ring, or a 5-5-5-, 5-5-6- or 5-6-6-fused tricyclic ring.

32. The method of claim 31 wherein the ring structure is a bicyclic or tricyclic ring structure and at least one ring of the ring structure is superimposable on the template space defined by at least one ring of the ring structure of the biologically active metallopeptide.

33. The method of claim 1 wherein the peptidomimetic comprises the formula: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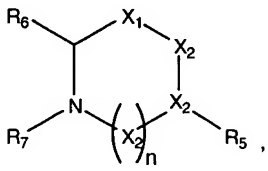
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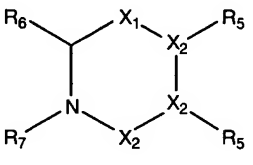
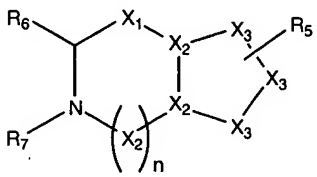

, or


wherein

X_1 is $(CH_2)_m$ or X_3;

X_2 is independently CH_2, CH, NH or N;

X_3 is independently $(CH_2)_n$, CH, NH, N, O, C=O, C=S, S, S=O, or SO_2;

R_5 is any moiety other than H;

R_6 is an amino acid side chain moiety or derivative thereof;

R_7 is one or more amino acid residues or derivatives thereof and optionally a terminal group moiety, or is an amino acid side chain moiety or derivative thereof;

R_7 and at least one of R_6 or R_5 each constitute an element occupying a similar descriptor space as corresponding elements of the biologically active metallopeptide;

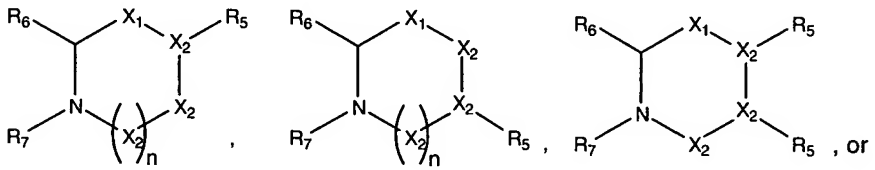
n is 0, 1, 2 or 3; and

m is 0 or 1;

provided that any two adjacent CH groups, adjacent NH and CH groups or adjacent NH groups may optionally form a double bond.

34. A peptidomimetic made by the method of claim 1.

35. The peptidomimetic of claim 34 comprising the formula: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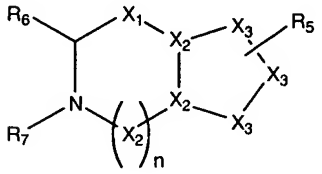
, or



wherein

X_1 is $(CH_2)_m$ or X_3;

X_2 is independently CH_2, CH, NH or N;

X_3 is independently $(CH_2)_n$, CH, NH, N, O, C=O, C=S, S, S=O, or SO_2;

R_5 is any moiety other than H;

R_6 is an amino acid side chain moiety or derivative thereof;

R_7 is one or more amino acid residues or derivatives thereof and optionally a terminal group moiety, or is an amino acid side chain moiety or derivative thereof;

R_7 and at least one of R_6 or R_5 each constitute an element occupying a similar descriptor space as corresponding elements of the biologically active metallopeptide;

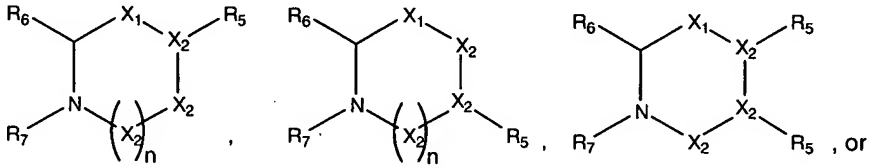
n is 0, 1, 2 or 3; and

m is 0 or 1;

provided that any two adjacent CH groups, adjacent NH and CH groups or adjacent NH groups may optionally form a double bond.

36. A peptidomimetic comprising a template space including a ring structure that is 5-, 6-, 7-, or 8-membered, 5-5-, 5-6-, 5-7-, 5-8-, 6-6-, 6-7-, 6-8-, 7-7-, 7-8-, or 8-8-fused bicyclic, or 5-5-5-, 5-5-6- or 5-6-6-fused tricyclic ring structure, and at least two descriptor spaces including elements that are amino acid side chain moieties or derivatives thereof joined by covalent bonds to the ring structure, wherein the descriptor spaces occupy a similar descriptor space as descriptor spaces defined by corresponding elements that are amino acid side chain moieties or derivatives thereof of a metallopeptide that binds to the same receptor as the peptidomimetic.

37. The peptidomimetic of claim 36 comprising the formula: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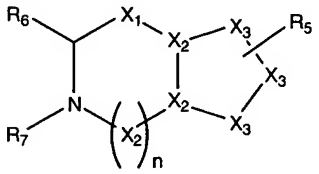


wherein

X_1 is $(CH_2)_m$ or X_3;

X_2 is independently CH_2, CH, NH or N;

X_3 is independently $(CH_2)_n$, CH, NH, N, O, C=O, C=S, S, S=O, or SO_2;

R_5 is any moiety other than H;

R_6 is an amino acid side chain moiety or derivative thereof;

R_7 is one or more amino acid residues or derivatives thereof and optionally a terminal group moiety, or is an amino acid side chain moiety or derivative thereof;

R_7 and at least one of R_6 or R_5 each constitute an element occupying a similar descriptor space as corresponding elements of the biologically active metallopeptide;

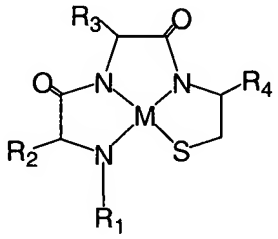
n is 0, 1, 2 or 3; and

m is 0 or 1;

provided that any two adjacent CH groups, adjacent NH and CH groups or adjacent NH groups may optionally form a double bond

38. A method of deriving a peptidomimetic of a biologically active metallopeptide comprising the steps of:

(a) selecting a biologically active metallopeptide with a ring structure defining a template space, the metallopeptide being of the formula:



wherein

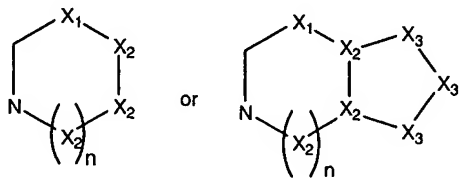
R_1 is at least one natural or unnatural L- or D-amino acid residues and optionally any terminal or capping group;

R_2 and R_3 are the same or different and independently selected from an amino acid side chain moiety or derivative thereof;

R_4 is any terminal or capping group and optionally any one or more natural or unnatural L- or D-amino acid residues; and

M is a metal ion;

(b) providing a non-peptidic ring structure superimposable on the template space defined by at least one ring of the ring structure of the biologically active metallopeptide, the non-peptidic ring structure being of the formula:



wherein

X_1 is $(CH_2)_m$ or X_3;

X_2 is independently CH_2, CH, NH or N;

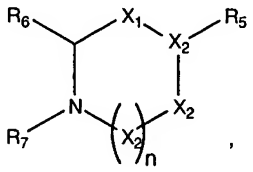
X_3 is independently $(CH_2)_n$, CH, NH, N, O, C=O, C=S, S, S=O, or SO_2;

n is 0, 1, 2 or 3; and

m is 0 or 1;

provided that any two adjacent CH groups, adjacent NH and CH groups or adjacent NH groups may optionally form a double bond; and

(c) adding at least three elements R_5, R_6, and R_7, to the non-peptidic ring structure, whereby a peptidomimetic of one of the following formulas results:



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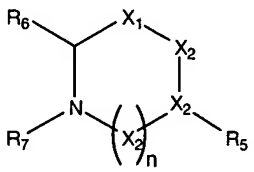

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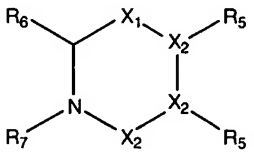
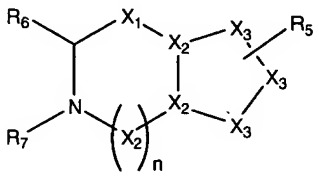


, or



wherein

R_5 is any moiety other than H;

R_6 is an amino acid side chain moiety or derivative thereof;

R_7 is one or more amino acid residues or derivatives thereof and optionally a terminal group moiety, or is an amino acid side chain moiety or derivative thereof; and

R_7 occupies a similar descriptor space as R_1 and at least either R_6 occupies a similar descriptor space as R_2 or R_5 occupies a similar descriptor space as R_3.

39. The method of claim 38 wherein R_7 is a functional or structural homologue of R_1, and at least either R_6 is a functional or structural homologue of R_2 or R_5 is a functional or structural homologue of R_3.

40. The method of claim 38, further comprising the step of comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide.

41. The method of claim 38 wherein the metal ion is an ion of V, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Y, Mo, Tc, Ru, Rh, Re, Pd, Ag, Cd, In, Sn, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Po, At, Sm, Eu or Gd.

42. The method of claim 38 wherein the biologically active metallopeptide binds to a target of interest.

43. The method of claim 42 wherein the target of interest is a receptor, antibody, toxin, enzyme, hormone, nucleic acid, intracellular protein domain of biological relevance or extracellular protein domain of biological relevance.

44. The method of claim 40 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises screening for binding to the target of interest of claim 43.

45. The method of claim 44 where screening comprises competing a known binding partner for binding to the target of interest with the peptidomimetic.

46. The method of claim 40 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises a functional assay.

47. The method of claim 40 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises a biological receptor capable of transmitting a signal, and comparing further comprises determining whether the peptidomimetic induces transmission of the signal.

48. The method of claim 40 wherein comparing the biological activity of the peptidomimetic to that of the biologically active metallopeptide comprises a biological receptor capable of transmitting a signal, and comparing further comprises determining whether the peptidomimetic inhibits transmission of the signal in the presence of a binding partner to the target of interest known to induce transmission of the signal.

49. The method of claim 38 wherein the peptidomimetic is specific for one or more melanocortin receptors, an angiotensin receptor, a vasopressin receptor an oxytocin receptor.

50. A method of deriving a peptidomimetic that binds to a target of interest comprising the steps of:

(a) selecting a known amino acid sequence with a known primary structure of n residues, where n is at least 4, which known amino acid sequence binds to the target of interest;

(b) designing a library of amino acid sequences by selecting at least two consecutive residues from a stretch of consecutive residues in the known primary structure and inserting a residue providing both an N and S for metal ion complexation on the carboxy terminal end of two of the at least two selected consecutive residues, or alternatively selecting at least three consecutive residues from a stretch of consecutive residues in the known primary structure and substituting a residue providing both an N and S for metal ion complexation for the carboxy terminal residue of any consecutive stretch of three of the at least three selected consecutive residues, each such sequence constituting a library member, wherein each library member differs by at least one residue or the location of the insertion of or substitution with the residue providing both an N and S for metal ion complexation;

(c) constructing the library of designed amino acid sequences;

(d) complexing each library member of designed amino acid sequences to a metal ion, thereby forming a library of metallopeptides wherein the metal ion is complexed to at least three atoms in the peptide sequence, such at least three atoms being part of at least two amino acid residues comprising the peptide sequence, whereby such at least three atoms and the metal ion form a ring structure comprising at least one ring, the at least one ring of the ring structure defining a template space;

(e) screening the library of metallopeptides for binding to the target of interest;

(f) selecting a metallopeptide exhibiting binding to the target of interest;

(g) modeling a non-peptidic ring structure that is superimposable on the template space defined by at least one ring of the ring structure of the selected metallopeptide; and

(h) forming a peptidomimetic by adding to the non-peptidic ring structure at least two elements independently comprising an amino acid residue, amino acid side chain moiety or derivative thereof, such at least two elements occupying a similar descriptor space as corresponding elements of the selected metallopeptide.

51. The method of claim 50, further comprising the step of comparing the biological activity of the peptidomimetic to that of the selected metallopeptide.

52. The method of claim 50, further comprising the step of comparing the biological activity of the peptidomimetic to that of the known amino acid sequence.

53. The method of claim 50 wherein the known amino acid sequence with a known primary structure of n residues is a peptide, a polypeptide or a protein.

54. The method of claim 50 wherein the library of designed amino acid sequences comprises at least one member wherein the residue providing both an N and S for metal ion complexation is the carboxyl terminal end residue of the amino acid sequence.

55. The method of claim 50 wherein the library of designed amino acid sequences comprises at least one member wherein the residue providing both an N and S for metal ion complexation is not the carboxyl terminal end residue of the amino acid sequence.

56. The method of claim 50 wherein the library of designed amino acid sequences comprises at least one member with at least four residues, wherein the residue providing both an N and S for metal ion complexation is inserted between two adjacent consecutive residues from a stretch of consecutive residues in the known primary structure.

57. The method of claim 50 wherein the residue providing both an N and S for metal ion complexation is an L- or D-3-mercapto amino acid.

58. The method of claim 57 wherein the L- or D-3-mercapto amino acid is L- or D-cysteine, L- or D-penicillamine, 3-mercapto phenylalanine, or a homologue of any of the foregoing.

59. The method of claim 50 wherein the metal ion is an ion of V, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Y, Mo, Tc, Ru, Rh, Re, Pd, Ag, Cd, In, Sn, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Po, At, Sm, Eu or Gd.

60. The method of claim 50 wherein the target of interest is a receptor, antibody, toxin, enzyme, hormone, nucleic acid, intracellular protein domain of biological relevance or extracellular protein domain of biological relevance.

61. The method of claim 50 wherein screening for binding to the target of interest comprises competing a known binding partner for binding to the target of interest with members of the library of metallopeptides.

62. The method of claim 61 wherein the known binding partner is the known amino acid sequence with a known primary structure of n residues.

63. The method of claim 50 wherein any cysteine residue in the library of amino acid sequences other than the inserted residue providing both an N and S for metal ion complexation is substituted with a homologue not containing a free sulfhydryl group.

64. The method of claim 63 wherein the cysteine is substituted with a glycine, alanine, serine, aminoisobutyric acid or dehydroalanine residue.

65. The method of claim 63 wherein the cysteine is substituted with an S-protected cysteine.

66. The method of claim 63 wherein the cysteine is substituted with a neutral mimetic of an amino acid residue of less than about 150 MW.

67. The method of claim 50 wherein the library of amino acid sequences is constructed by a chemical method of peptide synthesis.

68. The method of claim 50 wherein any proline residue in the two residues immediately adjacent the amino-terminus side of the residue providing both an N and S in any library member is substituted with a residue providing an N for metal ion complexation.

69. The method of claim 68 wherein the proline is substituted with a glycine, alanine, serine, aminoisobutyric acid or dehydroalanine residue.

70. The method of claim 68 wherein the proline is substituted with a neutral mimetic of an amino acid of less than about 150 MW and providing an N for metal ion complexation.

71. The method of claim 50 wherein if n is at least about 15 the method further comprises the step of dividing the primary structure into at least three divided primary structures, each such divided primary structure overlapping the primary structure of each adjacent divided primary structure by at least two residues, and thereafter following steps (b) through (f) with respect to each such secondary parent polypeptide.

72. The method of claim 50 wherein at least one residue of the selected at least two consecutive residues is a homologue of the corresponding residue in the stretch of consecutive residues in the known primary structure.